Zebrafish screen identifies novel compound with selective toxicity against leukemia.

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Scientific Abstract:
To detect targeted antileukemia agents we have designed a novel, high-content in vivo screen using genetically engineered, T-cell reporting zebrafish. We exploited the developmental similarities between normal and malignant T lymphoblasts to screen a small molecule library for activity against immature T cells with a simple visual readout in zebrafish larvae. After screening 26 400 molecules, we identified Lenaldekar (LDK), a compound that eliminates immature T cells in developing zebrafish without affecting the cell cycle in other cell types. LDK is well tolerated in vertebrates and induces long-term remission in adult zebrafish with cMYC-induced T-cell acute lymphoblastic leukemia (T-ALL). LDK causes dephosphorylation of members of the PI3 kinase/AKT/mTOR pathway and delays sensitive cells in late mitosis. Among human cancers, LDK selectively affects survival of hematopoietic malignancy lines and primary leukemias, including therapy-refractory B-ALL and chronic myelogenous leukemia samples, and inhibits growth of human T-ALL xenografts. This work demonstrates the utility of our method using zebrafish for antineoplastic candidate drug identification and suggests a new approach for targeted leukemia therapy. Although our efforts focused on leukemia therapy, this screening approach has broad implications as it can be translated to other cancer types involving malignant degeneration of developmentally arrested cells.